Spectrophotometric technology for the early detection of cutaneous melanoma

SPECTROPHOTOMETRIC TECHNOLOGY FOR THE EARLY DETECTION OF CUTANEOUS MELANOMA

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Abstract: This paper presents the design and experimental outcomes of an ongoing research project aimed at the early detection of melanoma by means of a new diagnostic device. This device, based on the principles of spectrophotometry, is expected to improve upon the current diagnostic methods, which are known to carry a margin of error quantified as 10-20%. This article presents the implemented technology, in the form of two scanning prototypes, the current experimental work, and the analysis procedures leading to the development of a diagnostic model based upon the spectral representation of pigmented lesions.

Keywords: Spectrophotometry, Principal component analysis, Image processing, Melanoma, Diagnostic methods

1. INTRODUCTION

Melanoma is a malignant tumor originating from particular types of cells named “melanocytes”, which are found at the skin and mucosal levels. The most established risk factors for the development of melanoma are sun exposition and burns. These are followed by another risk factor linked to the presence of benign pigmented lesions, namely moles, which may evolve into melanoma. Not only is melanoma a widespread tumor, but its incidence has dramatically increased over the past 30 years. The corresponding rate of increase shows no evidence of a stabilization trend. The incidence of melanoma in Europe is estimated as 12-14 cases/year/100,000 people. Incidence rates 3-4 times larger are observed in Australia and in the South-Western part of the U.S.A. An early detection of malignant lesions represents the essential means to considerably reduce both the mortality and the morbility of this illness.

The most accurate diagnostic method currently in use is dermatoscopy, or skin surface microscopy, which, in spite of a high diagnostic accuracy, carries a margin of error quantified as 10-20%. In order to target this margin and thereby reduce the corresponding mortality rate, an experimental research project, AISPEM, has been undertaken for the introduction of a new diagnostic method based on spectrophotometry. This article proposes the hardware instrumentation developed as part of the AISPEM project along with the results obtained to date.

2. SPECTROPHOTOMETRY

Reflective spectrophotometry or spectrophotometry is a hyperspectral imaging technique based on the measurement of the spectral reflection factor of the melanocytary lesion, as a function of the wave length of the incident radiation. Reflectance is a parameter measured as the intensity ratio between the reflected and the incident radiation, as a function of the wave length. In the reminder of this section we will explain the reasons for electing an image spectrophotometer (SPECIM ImSpector mod.V10) as a diagnostic device in the context of the AISPEM project.

The approach for the analysis and classification of a mole involves the acquisition of the corresponding spectral data in the visible (400-730 nm) and in the near-infrared (730-1000 nm) ranges: when suitably processed, these are both objective and independent of the measurement conditions. Additionally, spectral data provide a parametrization of the colour coordinates in compliance with the CIE LAB standard, as well as the possibility to extrapolate information on the energy absorption of the examined material at specified wave lengths.

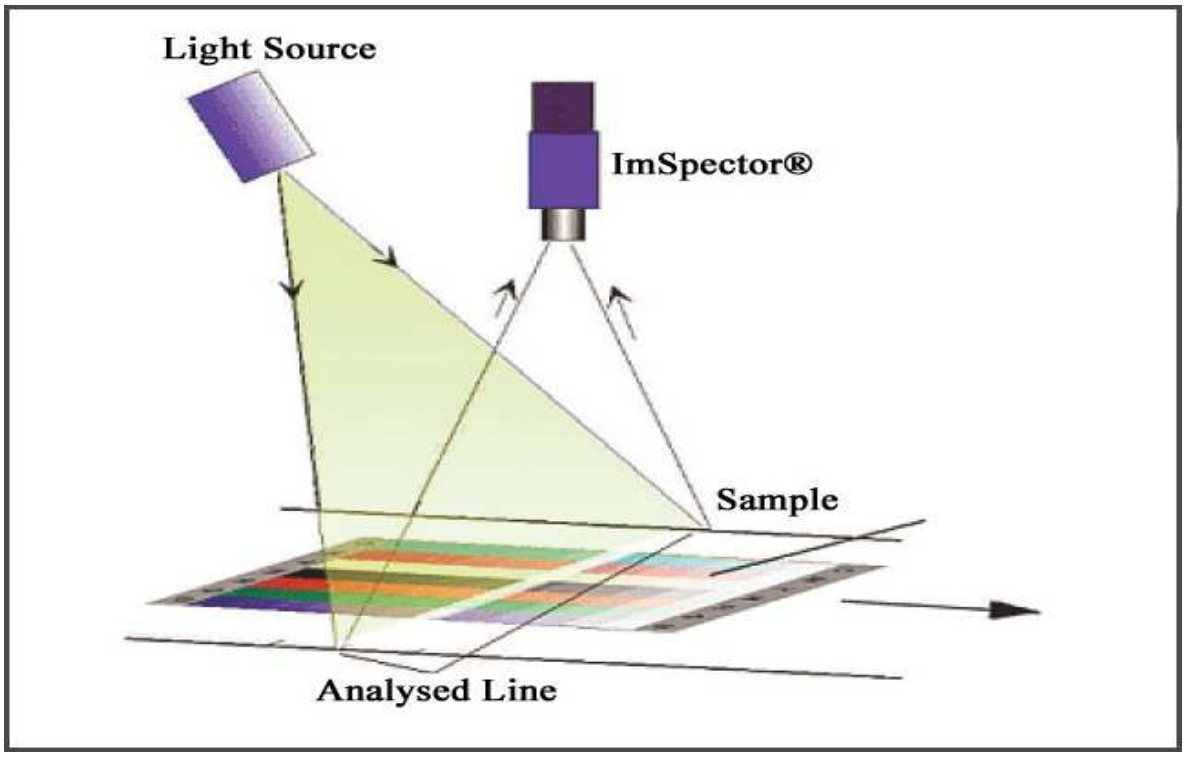

Figure 1: Features of the SPECIM ImSpector device

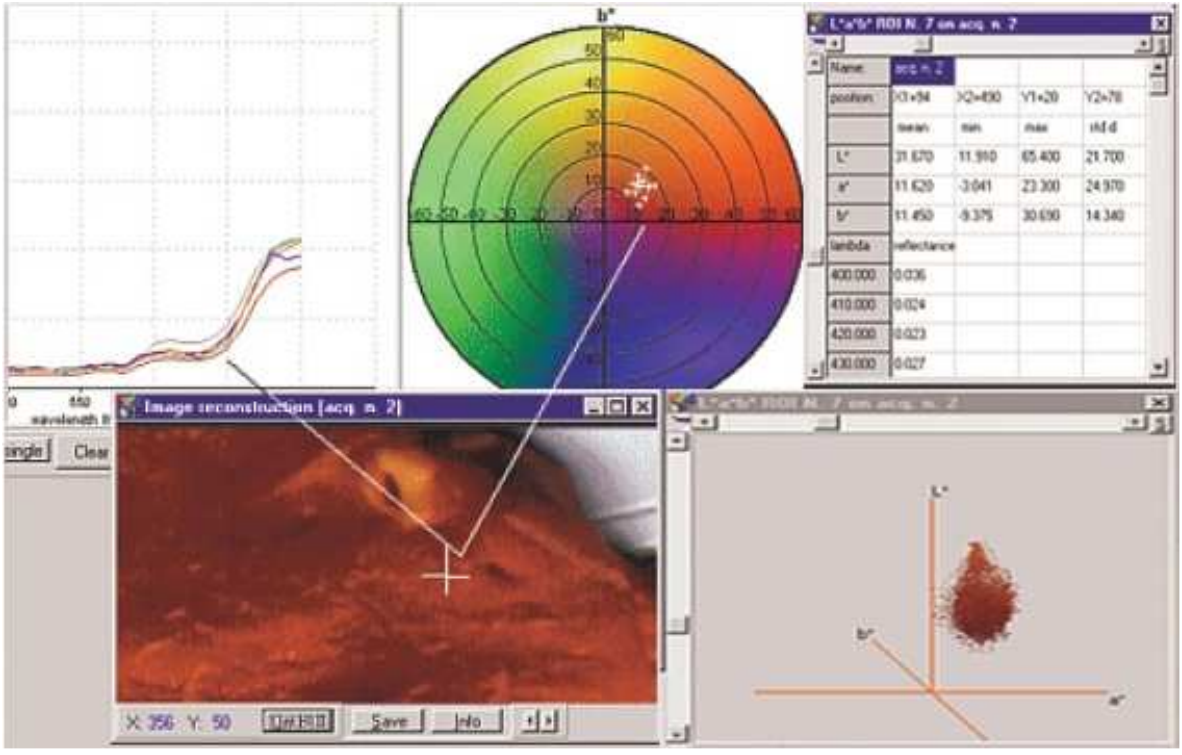

Figure 2: Example of pixel → spectrum correspondence

Unlike traditional spectrophotometers, which operate either on an individual point or on a small area of the sample at one time, the imaging spectrophotometer can acquire multiple points and provide multiple spectral profiles at the same time.
It is thus possible to produce a very detailed bi-

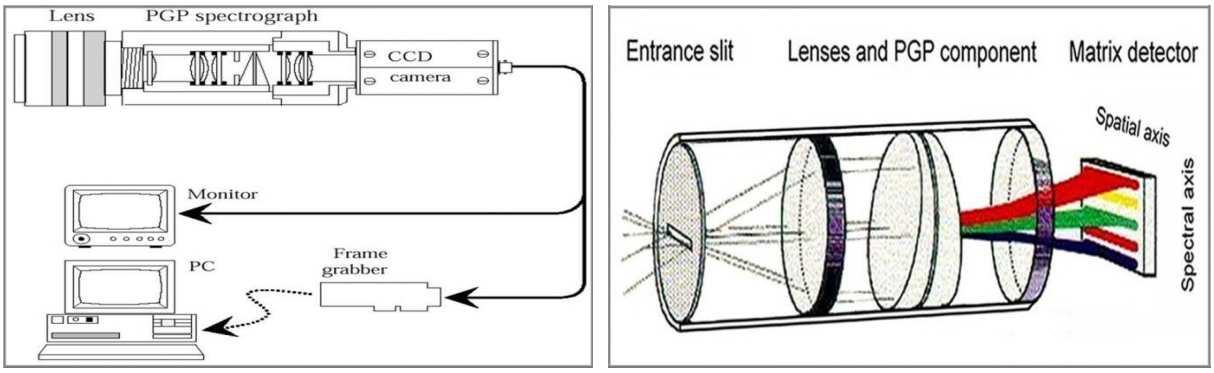

Figure 3: Spectrophotometer

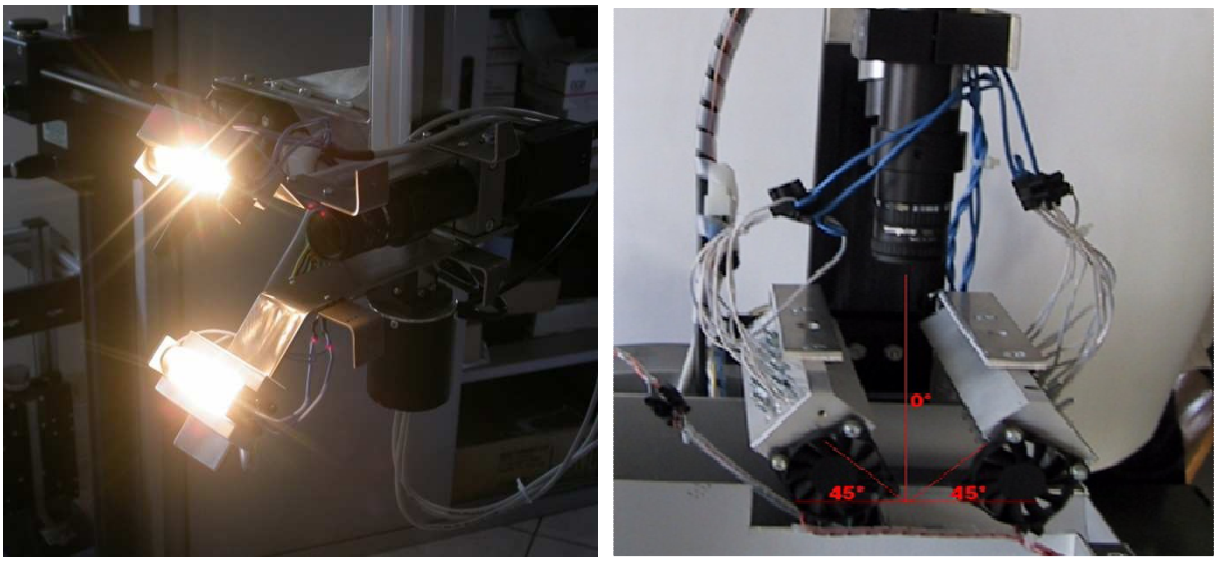

Figure 4: Visual configuration of source and sensor

dimensional scan of the sample; it is also possible to define an absorption/emission spectrum, covering the 400 to 1000 nm range of wave lengths, for each (x,y) pair of coordinates in the sample. The availability of this image-spectrum correspondence allows for the application of traditional image-processing algorithms, which can be used for instance to exclude less relevant or misleading points, to highlight areas of particular interest, or even to select very small irregular areas.

From a spatial standpoint, the resolution obtained through the operating room system (*off-line* device) is just under 0.1 mm. Instead the system used directly on the patient (*on-line* device) shows a resolution of approximately 0.14 mm.

A sample is scanned on a line by line basis and the scanning process requires the object or patient to remain still for a period of approximately 10 seconds. However, the motion of the sample does not determine an error in terms of spectral information. This would not be the case for a multi-spectral system: even with the use of filters, the latter would distort the spatial image making it visually unclear. Additionally, the image spectrophotometer shows a better resolution than the multi-filter system: its resolution, of approximately 3 nm, is more than adequate both for the extrapolation of colour features and for the detection of changes in absorbance at different wave lengths.

For scanning purposes the distance of the sample may vary between a few centimetres and a few metres, and in any case the process does not involve direct contact with the sample.

The visual configuration is of the 45/0 type: this means that the source is oriented at a 45º angle with respect to the sample normal and the sensor at a 0º angle (i.e. parallel to the sample normal). In practice two 45º sources are used to uniformly spread the light and to increase the intensity of the resulting signal.

From a structural standpoint the chosen spectrophotometer is especially well-suited for out-of-the-lab applications: the device is robust, compact and self-contained in size. Additionally, it hardly ever requires re-calibration due to misalignments of its lenses and inner mesh.

3. HARDWARE INSTRUMENTATION

The main objective of the AISPEM project is to develop and test an *on-line* diagnostic device, which requires the system to operate directly on the patient's skin. In order to meet this objective, a gradual approach has been adopted, involving the continual upgrade and improvement of the system.
An *off-line* prototype system was first set-up, capable of acquiring and storing the spectral images of surgically removed moles. The prototype has been installed and operated at the Istituto Scientifico Tumori (IST) of Genova, so that spectral acquisitions could be immediately performed on samples of tissues upon their surgical removal. Following the standard procedure, the samples are then sent for histological testing to ascertain their benign or malignant nature. Preliminary studies have been conducted on the spectral acquisitions obtained from samples of tissues after their histological analysis. Ongoing research based on these studies, has defined and is currently refining a set of spectral image processing algorithms for diagnostic applications.
A second prototype has also been built for the non-invasive acquisition of spectral data directly from the patient's skin – as this is the expected use of the device upon completion of the AISPEM project. With the new *on-line* prototype, the acquisitions are first performed *in vivo* on the patient, and subsequently repeated *ex vivo* on the excised tissue using the *off-line* prototype.
In the following sub-sections, we present the technical and functional details of the two prototypes: we also discuss their use in the surgical practice.

3.1 The *Off-line* Prototype

The *off-line* system allows for the spectrographic analysis of epidermic tissues (moles) as soon as they are excised. This way, information about the benign or malignant nature of the tumor can be gathered. During the first phase of the project, the results obtained from the spectrographic analysis of the tissues were compared to the results of traditional laboratory tests. This comparison allowed for the spectral analysis to be focused only on those samples of tissue recognized as melanoma. This choice was determined by the need to identify the key spectral parameters that are relevant in the diagnosis of melanoma.
The *off-line* system has been installed directly in the operating room, so that the sample tissues can be analyzed immediately after their excision. The core of this module consists of a light source, a spectrographic device, and a video-camera. These three main components are functionally linked within a mechanical device, which enables the motion of the sample for scanning purposes. The same device hosts the control electronics for this motion, the required light sources, and the spectrophotometer.
The sample, laid on glass, is placed onto a sliding support/tray, which translates according to user-specified parameters. This motion allows for the scanning of the sample, while the spectrophotometer remains in a fixed position. The dimensions of the unit are 500×300×500 mm, and its weight is approximately 20 kg (see figure 5).

3.2 The *On-line* Prototype

The *on-line* system is designed for the spectrographic analysis of epidermic tissues, namely moles, prior to their excision.
During the second phase of the project, the *on-line* acquisitions of mole images have been followed by *off-line* acquisitions for the same moles. A comparative study involving these two sets of acquisitions constitutes the basis for the ongoing identification of effective differences in the spectral behaviour of the sample between the *in vivo* and the *ex vivo* (excised) condition.
The *on-line* prototype has been installed in the same operating room where the *off-line* prototype is located, with the aims of both facilitating the acquisition procedures, and reducing any inconvenience caused to the patient (who does not need to be moved throughout the acquisition procedures). The *on-line* prototype consists of a scanning head attached to a mechanical support. The mechanical support includes a vertical shaft, equipped with wheels for ease of relocation, and a horizontal arm, which not only can be moved along and rotated about the shaft, but can also translate horizontally along its own axis. The scanning head is attached to one end of this arm by means of a rotational joint, which allows for its rotation around the axis of the supporting arm. The scanning head consists of a metallic screen enclosing the spectrophotometer, the required light sources, the directing laser sources, and the scanning mechanisms. When the *on-line* prototype is used, as opposed to the *off-line* one, the examined tissue is not moved. The user directs the spectrophotometer with the help of two collimating laser beams. During the scan the patient remains still, while the scanning head is translated as required.
The height of the vertical shaft is 200 cm, the length of the supporting arm is 150 cm, and the weight of the device is approximately 30 kg (see figure 6).

3.3 The Control Module

The control module is based on a workstation, which is linked to both of the acquisition prototypes. The workstation is equipped with a *frame-grabber* board for the digital acquisition of the images from either spectrophotometer, by means of a dedicated software tool.
A serial interface protocol (RS-232) links the control module to each spectral prototype. During the second phase of the project, the *on-line* acquisitions of mole images have been followed by *off-line* acquisitions for the same moles.

Figure 5: The *off-line* prototype

A comparative study involving these two sets of acquisitions constitutes the basis for the ongoing identification of effective differences in the spectral behaviour of the sample between the *in vivo* and the *ex vivo* (excised) condition.
The analysis strategy is focused on the entire spectrum of the acquired (and reduced) image, including the visible and near-infrared ranges of wave lengths, up to 1000 nm.
The process analyzes the set of spectra for the image pixels as a whole, and extracts a characteristic spectral profile known as the principal component. This profile best represents the reference, about which the variability of the (other) observed spectra can be expressed. In practice the principal component, multiplied by a suitable coefficient, approximates a punctual spectrum, which retains the maximum content of partial information. In other words, the principal component constitutes an approximation, which considerably reduces the volume of data to be analyzed. From an initial set of over 100 variables (namely the values of reflectance at the different wave lengths) a single numerical value is retained for each pixel, while preserving the core of the information content for the image as a whole.
The observed numerical values are used to produce a histogram of the image, which is then analyzed to identify the key macroscopic areas. Local minima in the histogram generally represent thresholds between different values. The image can be segmented on the basis of these thresholds: the resulting image involves a limited number of 'colours', and the regions characterized by rather homogeneous spectral features can easily be identified. It is up to the user to select the areas relevant to the lesion. The corresponding data, once isolated, are extracted and saved onto a file for further analysis.

4. DATA ANALYSIS

The process of analysis, as outlined in the previous section, aims to exploit the high spectral resolution of the acquisition technology built into the two prototypes. The idea is to analyze the whole set of data extracted both from the negative and from the positive cases, in order to develop a spectral model of the lesion. This model would be the reference for the assessment of new cases with the aim of determining the probability that their nature may be either benign or malignant.
The procedure is based on the Principal Component Analysis (PCA) technique, also used to reduce the number of working variables in the process of isolation of the lesion. The assumption behind this technique is that the most significant portion of the information content can be represented using a smal-

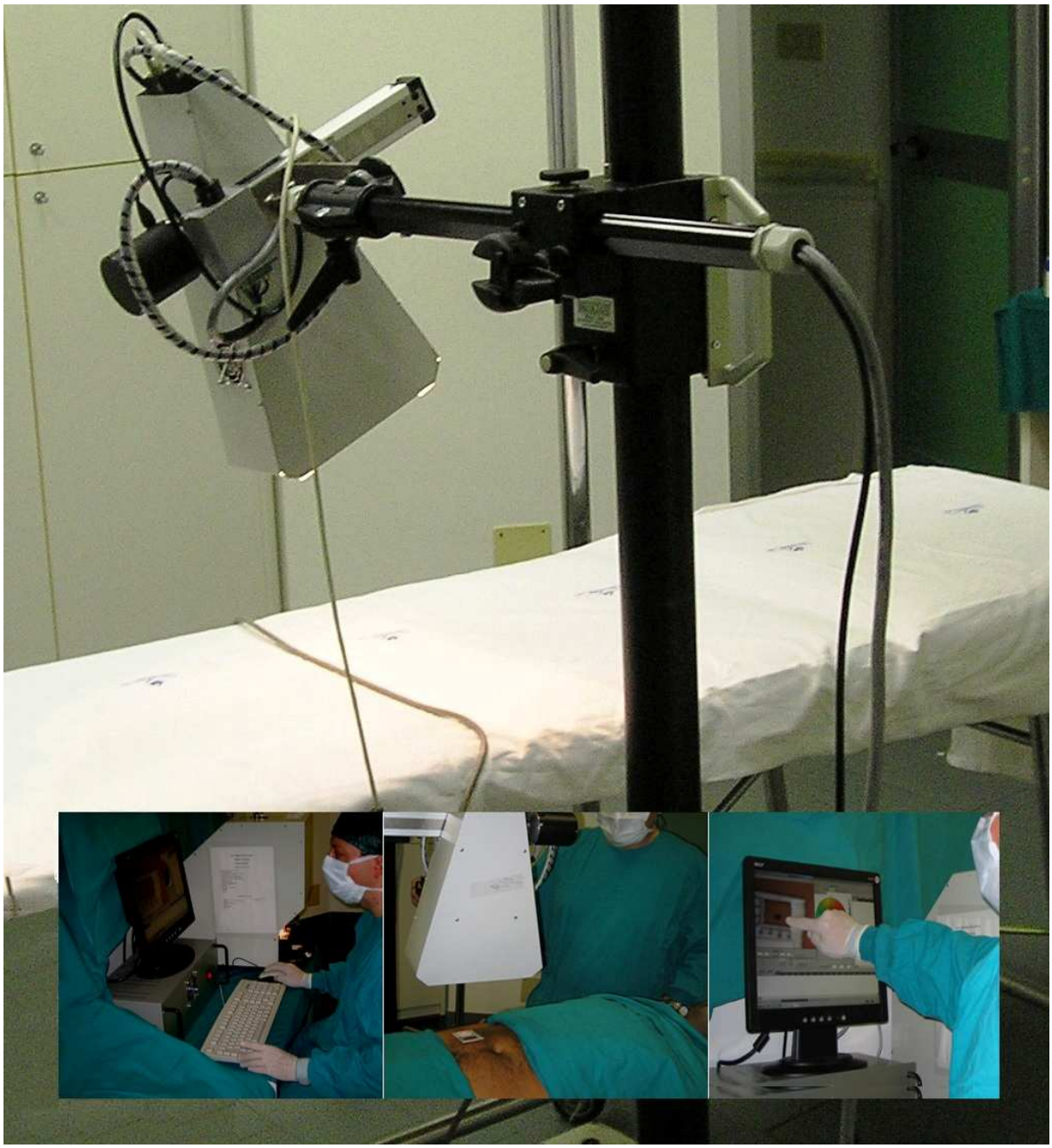

Figure 6: The *on-line* prototype

-ler number of variables than (the one) found in the raw data. The information content of the whole set of data can thus be expressed using a reduced number of dimensions, and whatever is left out of this representation carries a limited informative value.

In the specified application context, the set of spectral data generated through experimental acquisitions is represented as a set of vectors of size larger than 100 (one for each observed wave length). With the aid of the principal component technique, the size of these vectors can be dramatically reduced. In some cases the reduced vectors may include just 2 coordinates. These still account for over 95% of the global variance (which is a measure of the information content) observed in the original set.

The two coordinates of each reduced vector represent the coefficients needed to combine the two principal components and thus obtain an approximation of the original multidimensional vector.

The principal components involved in this combination are basic spectral profiles.

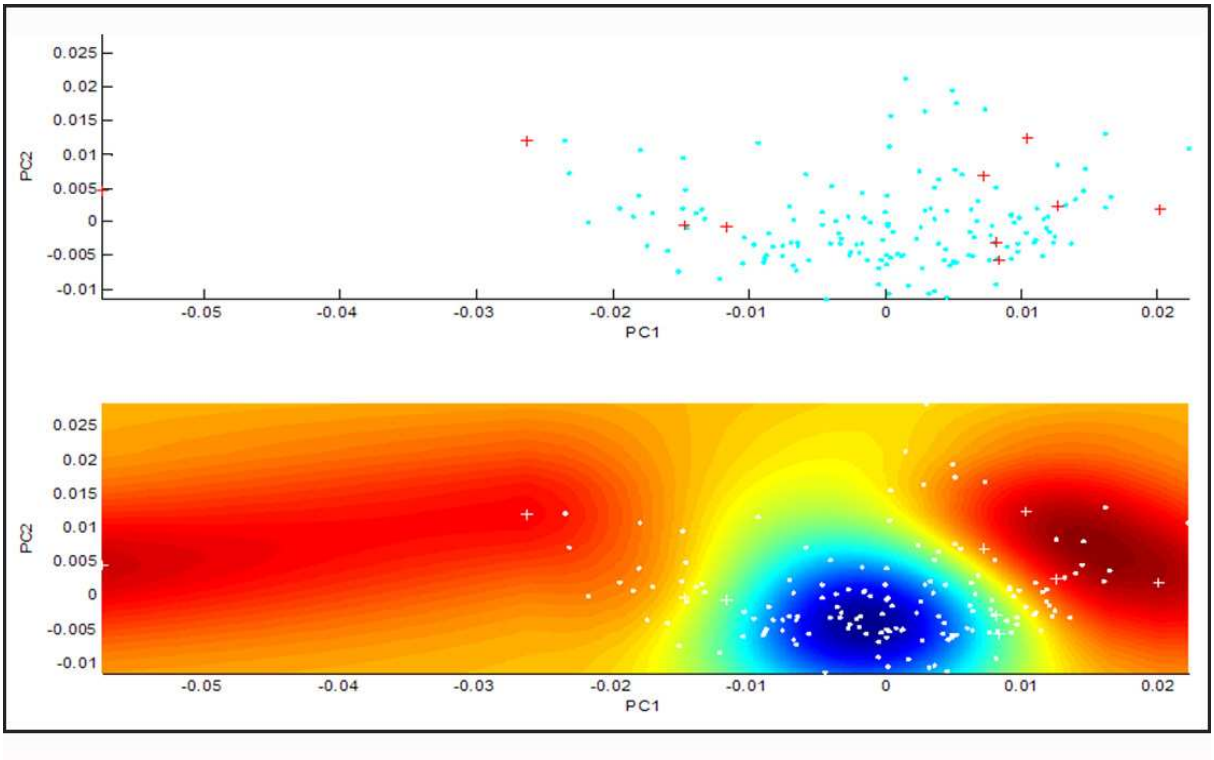

Figure 7: Distribution of the averages about the principal coordinates (top) and relative density of cases in the plane (bottom)

The two coordinates of each reduced vector represent the coefficients needed to combine the two principal components and thus obtain an approximation of the original multidimensional vector. The principal components involved in this combination are basic spectral profiles.

Once the data are reduced to two dimensions, they can be represented on a Cartesian plane. In such a plane the regions where particular types of data are predominant over other types may be identified. In such conditions the principal components could be assumed as a suitable model for the data set: any new case would be expressed by means of two coefficients, which would be used as coordinates to identify a point in the plane. The location of this point in the plane would fall within one of the identified regions: the probability for the case to share the characteristics of the dominant type in that region could then be estimated. Figure 7 presents the model obtained on the basis of the data currently available. The top part of the figure illustrates the distribution of the averages of negative (blue points) and positive (red crosses) cases about the two principal components (accounting for 95.7% of the global variance). The bottom part of the figure shows the relative density of cases in the plane: bluer shades indicate a higher concentration of negative rather than positive cases.

The limited number of positive cases acquired this far does not yet allow for reliable statistical estimates of the probability that a case may be benign or malignant.

As shown in figure 7, only 10 positive acquisitions are available against 149 negative ones.

The distribution of the cases examined to date suggests the presence of a ‘zone’ in the plane where positive cases are unlikely to occur (the blue zone in figure 7). This preliminary result indicates the future possibility of classifying as clearly benign some of the cases that are currently judged as uncertain (prior to histological testing). In order for this hypothesis to be confirmed, statistical validation will be required on a sample including a much larger number of positive cases.

5. FURTHER DEVELOPMENTS: TELE-MEDICINE APPLICATIONS

Based on the knowledge recently built within other projects, an embryonic information network has been developed for the purposes of telemedicine applications. Such a network is intended for facilitating the exchange of data and information among different centres, which deal with the acquisition and study of data acquired using the AISPEM system.

The network, still at the embryonic stage, was initially designed assuming two remote locations (for instance a specialistic centre and an individual

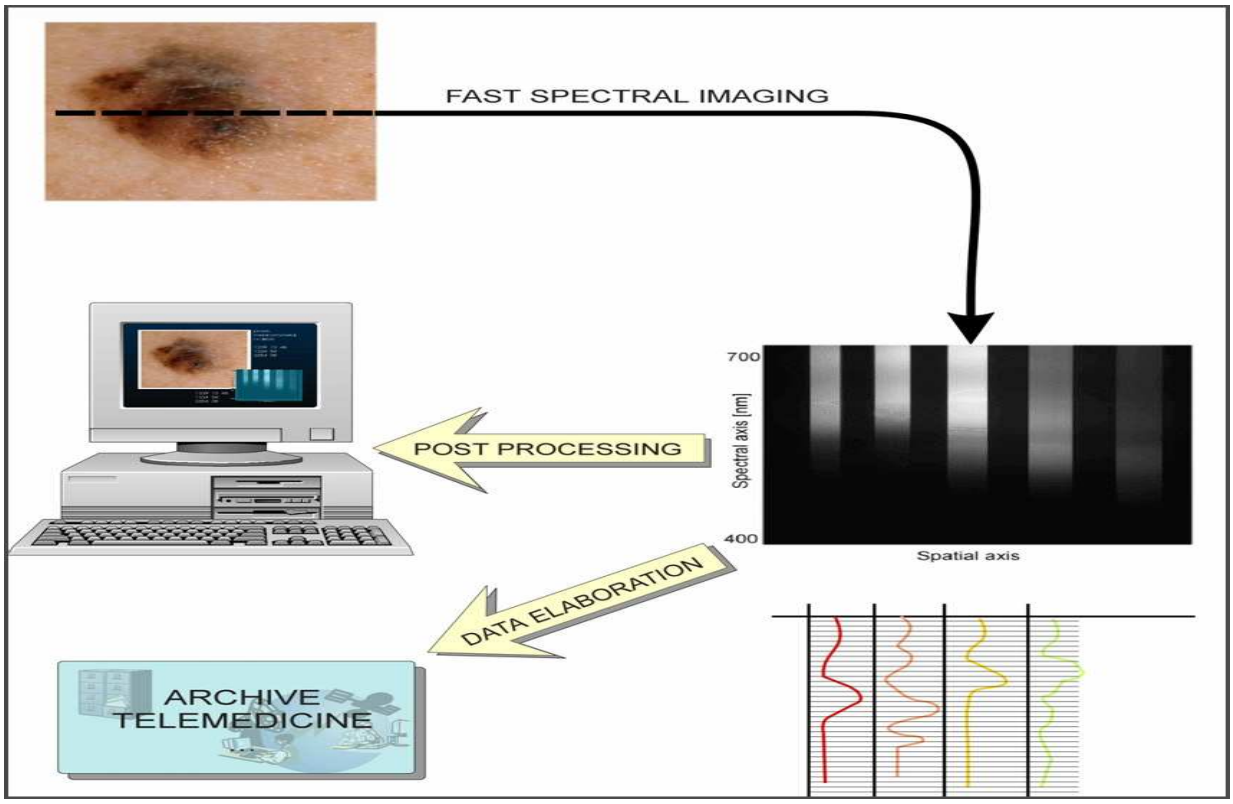

Figure 8: Telemedicine applications

GP within a local medical practice) which can be connected via the Internet for audio-visual communication, with the option of sharing files and applications.
The system, equipped with high definition webcams (such as Canon Osprey), an audio portal, a commercial videoconferencing application, and a software package for the remote management of medical data, is currently being validated for its use in telemedicine applications. Early tests have produced very promising results in terms of both system performance and ease of use. Figure 8 illustrates an application of the AISPEM system in the telemedicine context.

6. CONCLUSION

This article has reported on the development activities undertaken, and on the experimental results obtained as part of the AISPEM project. The project is aimed at the implementation and experimental validation of a new diagnostic device for the early detection of melanoma. Two prototype devices, intended for *on-line* and *off-line* use respectively, were built as part of this project. Both prototypes are based on spectrophotometric technology and are aimed at the development of an effective diagnostic model. The *on-line* prototype, capable of acquiring spectrographic images directly from the patient's skin, was finalized in February 2006. In order to improve on the current set of diagnostic/comparative parameters, images of the sample moles have been acquired both prior (*on-line* prototype) and immediately after (*off-line* prototype) their excision. *Off-line* acquisitions started in December 2004, while the *on-line* prototype become operational at the end of February 2006. Both the *in-vivo* and the *ex-vivo* acquisitions of moles are still ongoing.
The number of images relevant to the positive cases detected to date is just 13, out of a set of 400 examined cases. The very limited number of positive cases acquired this far does not yet allow for reliable statistical estimates of the probability that a given case may be of benign or malignant nature.
However, the distribution of these cases suggests that a particular area of the density plane (the blue zone in figure 7) corresponds to a very low probability of occurrence for positive cases. In order for this statement to be fully supported and verified, statistical validation will be sought on the basis of a much larger set of positive cases.
The preliminary results obtained this far, have led to a number of considerations, which are summarized in the following. It is expected that the introduction of the new diagnostic system at the clinical level will have a positive cost-benefit impact both on the patient and on the National Health Services (SSN). Specifically, wait times will be reduced and resources will be better allocated within specialistic structures. Additionally, the patient's experience will

typically be less stressful as s/he would be directed to specialistic centres only when strictly needed.

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